## Cardiovascular risk and inflammation

van Halm, V.P.

2008

# Summary

## Scope of this thesis

In this thesis the cardiovascular risk in rheumatic diseases is investigated against the background of mounting evidence revealing the pivotal role of inflammation in the development of cardiovascular disease (CVD). The chronic inflammatory nature of rheumatic diseases, such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS), raises the question whether the increase in inflammatory burden causes a higher prevalence of CVD.
Moreover, in this thesis epidemiological associations between inflammation and CVD are studied, trying to elucidate possible causal pathways. The focus of this thesis is on established cardiovascular risk factors such as dyslipidemia and thyroid dysfunction in rheumatic diseases. Furthermore, disease associated variables such as antibody formation and anti-rheumatic treatment, that might be responsible for an increase in cardiovascular risk in rheumatic diseases are investigated.
In the final paragraphs of this thesis the generalisability of the main findings are addressed and recommendations for future research of CVD in rheumatic diseases are given.

## Main findings

In **chapter 2** results of the CARRÉ study, an ongoing study into CVD in RA, are presented. The prevalence of CVD and its risk factors in RA-patients is studied and compared to healthy individuals and individuals with impaired glucose metabolism. In total 755 participants were included, 353 RA-patients, 258 healthy individuals and 194 diabetes mellitus type 2 (DM2) patients, respectively. The prevalence of CVD and its risk factors were compared per group and the odds ratios for CVD were calculated.
Hypertension and smoking, were observed more frequently in RA-patients compared to healthy individuals. On the other hand other cardiovascular risk factors, such as dyslipidemia, were found less often in RA-patients. The prevalence for CVD in RA-patients was approximately 13 %, which is two to three fold that of healthy individuals. Furthermore, the observed cardiovascular risk in RA at least equals the risk found in DM2-patients, which does not change after adjusting for age, gender, hypertension, dyslipidemia and smoking, indicating that RA is an independent risk factor for CVD.

An important well established risk factor for CVD is dyslipidemia. Some authors have suggested that inflammation can cause a deterioration of the lipid profile. Whether this association between inflammation and dyslipidemia exists and if so to what extent, is investigated in **chapters 3 and 4**.
In **chapter 3** the relationship between inflammation parameters and lipid levels in 45 AS-patients participating in a phase 2 trial into the safety and efficacy of leflunomide, is assessed. It was shown that increases in disease activity are associated with decreases in lipid levels. Moreover, the decrease in the anti-atherogenic high density lipoprotein cholesterol (HDLc) tends to be almost twice as large as the decrease in total cholesterol (TC), resulting in a more atherogenic lipid profile. The magnitude in which disease activity influences lipid levels is limited.
Although the observed influence of inflammation of lipid levels is small, this limited worsening of the lipid profile may have a clinically important impact on the cardiovascular risk in view of the chronic nature of rheumatic diseases.

In **chapter 4** the effect of powerful immunosuppression on the lipid profile is studied in 80 consecutive RA-patients. These patients received anti-tumor necrosis factor-α treatment in the form of periodic infliximab (IFX) infusions for a total period of one year. During this year the course over time of the lipid levels and their relationship with inflammatory parameters and prednisone dosages were studied.
It was shown that IFX treatment causes reduction in disease activity, with concomitant decrease in prednisone dosages. Furthermore, lipid levels initially improved, however, at the end of the study the lipid changes normalised. Longitudinal analyses revealed a significant association between lipid levels and inflammation parameters which is in line with chapter 3 of this thesis. Furthermore, a significant inverse association was found between lipid levels and prednisone dosages. No changes in lipid levels were observed after 48 weeks of immunosuppressive treatment which is thought to be caused to the opposing effects of inflammation and prednisone dosage on the lipid profile.
The worsening effect of inflammation on the lipid profile, as demonstrated in chapters 3 and 4, is a possible pathway between inflammation and CVD in patients with rheumatic diseases.

**Chapter 5** is a study of the lipid profile in the pre-clinical phase of RA, before the start of the symptoms. Earlier studies in this pre-clinical phase had shown that future RA-patients formed more antibodies and had elevated inflammation parameters. This combined with the studies described in chapters 3 and 4 showing that inflammation deteriorates the lipid profile, the study in chapter 5 was done to investigate when the worsening of the lipids, compared to healthy controls, starts.
The lipid levels of 1078 deep frozen, serial samples of 79 non-related RA-patients were compared to 1071 control sera, which were matched for age, gender and storage time and condition. A median of 13 samples per RA-patient was recovered with the first sample taken at a median of 7.5 years before the onset of symptoms.
Comparison of the future-RA and non-RA sera revealed that up to at least 10 years before the symptoms onset, future-RA patients displayed, on average, 4% higher TC, 9% lower HDLc, 17% higher triglyceride and 6% higher apolipoprotein B levels compared to matched controls ($p \leq 0.05$). In line with the results found in chapters 3 and 4, only a small part of the differences in lipid levels between future-RA and non-RA could be explained by inflammation parameters. For example, only 3.6% of difference between groups in HDLc levels was explained by C-reactive protein (CRP) levels.
Chapter 5 supports the impression that inflammation enhances cardiovascular risk through altering the lipid profile. However, because the deterioration and the differences between future-RA and non-RA were small the results of this study leaves room for various other ways by which inflammation could alter cardiovascular risk.

In addition to dyslipidemia thyroid disorders, particularly hypothyroidism, are well established risk factors for CVD. In **chapter 6** the prevalence of thyroid disorders and its relation with cardiovascular risk in RA is investigated. The study in this chapter uses the dataset from the CARRÉ study described in chapter 2. Of all the participants the thyroid status is established and subsequently compared to the population at large. Furthermore, an assessment of the cardiovascular risk per group was done, correcting for other conventional cardiovascular risk factors as diabetes, hypertension and dyslipidemia.

It is shown that clinical hypothyroidism is found three times more often in female RA-patients than in the general population. Furthermore, these women have a fourfold higher risk for CVD in comparison with euthyroid RA-patients.
This study shows that in addition to dyslipidemia, thyroid disorders also play an important role in the enhanced cardiovascular risk of patients with rheumatic diseases, such as RA.

A subset of 192 RA-patients from the CARRÉ database was used for **chapter 7**. In this chapter a non-conventional risk factor for CVD, antibody formation against human 60-kDa heat shock protein (HSP60), is investigated. Heat shock proteins protect endothelial cells against denaturation caused by harmful influences such as oxidising agents, dyslipidemia, hypertension and certain agents in cigarette smoke. Patients with rheumatic disorders are known to form more antibodies than healthy individuals, for example against citrinullated peptides. Therefore, in theory RA-patients could form more antibodies against HSP60, counteracting or even eliminating HSP60 and subsequently develop more CVD. Chapter 7 shows that although RA-patients have higher titres of HSP60-antibodies than healthy controls, nor the height, nor presence of these antibodies was associated with prevalent CVD. Therefore, in this study the increased cardiovascular risk in RA can not be explained through formation of antibodies against HSP60.

In addition to naturally occurring influences on established and newer risk factors for CVD, influences on the cardiovascular risk in rheumatic diseases caused by treatment, should be considered. That is why **chapters 8 to 10** address the influence of anti-rheumatic treatment on the risk for CVD. The first of these chapters provides an overview of the literature on the risk for CVD associated with agents prescribed in osteoarthritis and rheumatoid arthritis (**chapter 8**).

**Chapter 9** reports the findings of a case control study of 5649 patient-years in 613 RA-patients, 72 with CVD and 541 without CVD. Data on RA, CVD and drug treatment were evaluated from time of RA-diagnosis up to the first cardiovascular event or the end of the follow-up period. The dataset was categorised according to use of disease modifying anti-rheumatic drug (DMARD), sulfasalazine (SSZ), hydroxychloroquine (HCQ), methotrexate (MTX) or combinations of time. Subsequently, per DMARD-group odds ratios for CVD in comparison with RA-patients who never used SSZ, HCQ or MTX, corrected for age, gender, smoking and RA-duration, were calculated.
A significant reduction in the risk for CVD in the treatment groups that included treatment with MTX and to a lesser extent SSZ, was observed. This reduction remained after additional adjustment for hypertension, diabetes, hypercholesterolemia, the presence of rheumatoid factor positivity and erosion(s) on radiographs. It is hypothesised that treatment with conventional DMARDs, particularly MTX, slows down atherosclerosis through suppression of inflammation, which results in a decreased risk for CVD.

**Chapter 10** describes an open pilot study in which 15 consecutive AS-patients were followed for 6 months, starting with 3 months of rosuvastatin therapy followed by a 3 months observational period. Assessing various disease activity parameters in these patients showed improvement during statin therapy illustrated by a significant reduction of acute-phase-reactants such as CRP and ESR.

This study enforces the pleiotropic effects of statins by showing a decrease in disease activity in patients receiving the active compound compared to patients who do not. These results demonstrate that administering statins to patients with rheumatic diseases because of their increased cardiovascular risk, could also have a beneficial effect on the rheumatic disease itself.

## Generalisability

In this thesis a significantly increased cardiovascular risk in patients with chronic inflammatory rheumatic diseases such as RA and AS is shown. Furthermore, this thesis advocates that this increase is caused partially by worsening of the cardiovascular risk profile and partially by a direct pro-atherogenic effect of inflammation, the distinctive feature of rheumatic diseases.
The worsening effect on the cardiovascular risk profile is supported in this thesis by demonstrating that inflammation deteriorates lipid levels, thus increasing the risk for CVD. Moreover, the heightened immune response in RA seems to be related to a higher prevalence of clinically overt hypothyroidism with a subsequently increased cardiovascular risk.
This thesis also addresses the possibility of direct pro-atherogenic effect of inflammation, the most prominent characteristic of rheumatic diseases. The inflammatory character of rheumatic diseases is thought to cause accelerated atherosclerosis with more and less stable plaque formation in arteries. This thesis supports this harmful effect of inflammation by showing that suppression of inflammation lowers the cardiovascular risk, which remains even after correcting for conventional cardiovascular risk factors.

One should see a rheumatic, inflammatory disease as an independent risk factor for CVD, as diabetes mellitus is known to be. When this is more widely accepted this will have consequences on the management of patients at risk for CVD. Furthermore, this increased risk should encourage active treatment of the rheumatic disease itself. Lowering inflammation appears to, at least, slow down the build up of atherosclerosis in arteries and could subsequently decrease the prevalent CVD.

This thesis points to inflammation as the major cause of the enhanced cardiovascular risk in rheumatic diseases. One could generalise this to all inflammatory diseases and events. In support of such a generalisation are several studies demonstrating that people with chronic inflammatory periodontal diseases, such as gingivitis, suffer greater risk for getting CVD. However, the fact that the inflammatory processes in rheumatic diseases are autoimmune driven may make it impossible to extrapolate the findings of this thesis to all inflammatory events. Furthermore, RA and AS are diseases with high-grade inflammation and it is not sure whether low-grade inflammation has similar associations with CVD and its risk factors.

## Future perspectives

Future research has to be done to further elucidate the pathway, or many pathways by which inflammation causes an enhanced risk for CVD. This should be done by a combination of both laboratory research and epidemiological studies. Meanwhile, one feels that it would be prudent for any clinician to be aware of the association between inflammation and CVD.

With awareness comes planning for the future. The next logical step for future research, would be to start mapping the cardiovascular risk profile of patients with chronic inflammatory diseases such as RA and AS. Besides registration of events and risk factors it should be investigated whether or not the elevated risk can be diminished by therapeutic interventions.
This raises the question how this research should be done. The most feasible setup would be a large outpatient setting. All patients with a rheumatic disease would be followed at regular intervals to record variables related to cardiovascular risk and related to the rheumatic disease. Within this setting it would be possible to investigate whether (intensive) treatment of cardiovascular risk factors reduces cardiovascular risk. Ideally this would be done in a double blind placebo controlled fashion, whether this is feasible is questionable. A fortunate finding, shown in this thesis, for when interventions are being explored, is that treatment with statins to lower cholesterol levels, could also have a beneficial effect on the rheumatic disease itself.

## Conclusions

In conclusion, since in 1999 the author Russel Ross stated in a leading journal that atherosclerosis should be seen as an inflammatory disease, there have been many articles published on this topic. However, several important questions regarding the relationship between CVD and inflammation, remain to be answered. Nevertheless, one could speculate and make an addition to the statement by Ross and state:

*"Atherosclerosis is an inflammatory disease and inflammatory diseases are atherogenic."*

After reading this thesis three messages should stand out. Firstly, rheumatologists should be aware of the increased risk for CVD in their patients and so they should easily be convinced to actively screen their patients for CVD and cardiovascular risk factors. Secondly, cardiologists should be able to see that rheumatic inflammatory diseases are important independent risk factors for CVD. Thirdly, besides awareness of clinicians, patients should be made aware of the increased cardiovascular risk associated with rheumatic diseases, so they can take the appropriate measures to try to minimise their cardiovascular risk for the future.